REMARKS

Applicant has amended claim 18 in order to expedite prosecution in this matter. Support for this amendment can be found throughout the specification, particularly at page 13, lines 13-17 and the examples. Accordingly, no new matter has been added, and the entry of the amendment is respectfully requested.

Applicant appreciates the Examiner's indication that claim 14 would be allowable if rewritten in independent form including all limitations of the base claims and any intervening claims. Applicant has rewritten claim 14 to incorporate the recitations of claims 1 and 13. As such, this amendment does not introduce new matter and its entry is respectfully requested.

Claims 1, 4, 13, 16-20, and 22-23 were rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description.

Applicant respectfully disagrees and submits that the rejection be withdrawn for the following reasons.

The applicant respectfully submits that they have provided, as of the filing date, a precise definition of the claimed invention so as to distinguish it from others and such that the skilled artisan knows what is being described. The cases cited by the Examiner, namely <u>Enzo Biochem.</u> and <u>Lilly</u>, refer to inventions of nucleic acids. The claims in the present application refer to antibodies. Antibodies are treated differently from nucleic acid as is evidenced by a comparison of the field, and an examination of patents. For example, nucleic acids are typically defined by Sequence Identifiers, whereas antibodies are typically defined functionally by what antigen they bind to.

Indeed, in Capon v. Eshhar, (Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005)), attached herewith as Exhibit A, the Court specifically held:

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Id. at 1358.

The Court went on to distinguish the involved case from Lilly [relied upon here by the Examiner] and looked at what the discovery was. In Lilly, the discovery was the function of a gene and therefore its DNA sequence was critical. In Eshhar, the discovery was not gene function, but rather the use of a particular combination of genes. Thus, the Court held that the DNA structure in Eshhar was not necessary. Similarly, here, the involved claims in the present invention are directed to a diagnostic method utilizing an antibody, **NOT** to the discovery of the antibody itself.

The Examiner acknowledges that the Applicant has satisfied the written description requirement with regard to a class of antibodies that selectively binds to human Mi, namely "an epitope in the N-terminus Taq-Sac fragment of human Mi". Applicant was in possession of an antibody which selectively binds human Mi. The Examples detail the methods by which the antibody was created and validated (e.g. to ensure that it selectively bound to Mi and not other potential targets). The skilled artisan, following these methods, would be able to produce antibodies that selectively bind human Mi.

Genetic manipulation of antibody genes was routine to those of skill in the art as of the effective filing date of the present application (i.e. January 1998). As support for such, Applicants attach a list of abstracts, all published prior to the filing date of the present application, that detail that a description of **function** defines an antibody to the skilled artisan prior to 1998 because they knew its critical characteristic (Exhibit B). The skilled artisan clearly

knows, for example, that an antibody raised against peptides comprising regions unique to human Mi that selectively binds human Mi describes a definite type of antibody. Methods are also taught in the instant application to test whether this antibody would function in its intended use (i.e. diagnostically), see, for example, page 19, lines 25-34. Thus, the present description clearly provides a written description to a person of ordinary skill in the art of what the Applicant has claimed in the rejected claims.

Claims 18-23 were rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description.

Applicants respectfully submit that the amendment to claim 18 makes explicit that which was implicit, and has obviated the rejection. In particular, Applicant has amended claim 18 to recite that the antibody is <u>raised against peptides comprising regions</u> unique to human Mi that binds human Mi. This is the language specifically used at page 13, lines 13-17.

Accordingly, in view of the foregoing, applicants respectfully submit that all claims comply with 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

Date: January 31, 2006

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DANIEL J. CAPON, ARTHUR WEISS, BRIAN A. IRVING, MARGO R. ROBERTS, and KRISZTINA ZSEBO, Appellants, v. ZELIG ESHHAR, DANIEL SCHINDLER, TOVA WAKS, and GIDEON GROSS, Cross-Appellants, v. JON DUDAS, Director of the Patent and Trademark Office, Intervenor.

03-1480, 03-1481

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

418 F.3d 1349; 2005 U.S. App. LEXIS 16865; 76 U.S.P.Q. (BNA) 1078

August 12, 2005, Decided

PRIOR HISTORY: [**1] Appealed from: United States Patent and Trademark Office Board of Patent Appeals and Interferences. (Interference No. 103,887)

CASE SUMMARY:

PROCEDURAL POSTURE: Both parties to a patent interference proceeding between United States Patent No. 6,407,221 ('221 patent) and patent application Serial No. 08/084,994 ('994 application) appealed the decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office that the specification of neither party met the written description requirement of the patent statute, dissolving the interference and cancelling the claims.

OVERVIEW: The patent and application were directed to the production of chimeric genes designed to enhance immune responses. The Board held that neither party's specification provided the requisite description of the full scope of the chimeric DNA or encoded proteins. The Board Director argued that it could not be known whether all of the permutations and combinations covered by the claims would be effective for the intended purpose, and that the claims were too broad because they might include inoperative species. Both parties presented specific examples of the production of specified chimeric genes. The court held it was not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. The court held that the Board erred in ruling that 35 U.S.C.S. § 112 imposed a per se rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence was already known in the field.

OUTCOME: The Board's decision was vacated and the case remanded to the Board for further proceedings.

LexisNexis(R) Headnotes

Administrative Law > Judicial Review > Standards of Review > Arbitrary & Capricious Review

[HN1] In accordance with the Administrative Procedure Act, the law as interpreted and applied by an agency receives plenary review on appeal, and the agency's factual findings are reviewed to determine whether they were arbitrary, capricious, or unsupported by substantial evidence in the administrative record.

Patent Law > Claims & Specifications > Definiteness > Precision Standards

[HN2] The required content of a patent specification is set forth in 35 U.S.C.S. § 112. The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Patent Law > Claims & Specifications > Definiteness > Precision Standards

[HN3] The "written description" requirement of 35 U.S.C.S. § 112 implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the

patentee was in possession of the invention that is claimed.

Patent Law > Claims & Specifications > Description Requirement > General Overview
[HN4] It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which an inventor is entitled. Such a decision usually focuses on the exemplification in the specification.

Patent Law > Claims & Specifications > Description Requirement > Proof
[HN5] The determination of what is needed to support generic patent claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Patent Law > Claims & Specifications > Description Requirement > Proof
[HN6] It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.

Patent Law > Claims & Specifications > Description Requirement > Written Description Versus Enablement
[HN7] Although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements.

Patent Law > Claims & Specifications > Description Requirement > Proof
[HN8] The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention.

COUNSEL: Steven B. Kelber, Piper Rudnick, LLP, of Washington, DC, argued for appellants.

Roger L. Browdy, Browdy and Neimark, P.L.L.C., of Washington, DC, argued for cross-appellants.

Mary L. Kelly, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Arlington, Virginia, argued for intervenor. With her on the brief were John M. Whealan, Solicitor and Stephen Walsh, Associate Solicitor.

JUDGES: Before NEWMAN, MAYER, * and GAJARSA, Circuit Judges.

* Haldane Robert Mayer vacated the position of Chief Judge on December 24, 2004.

OPINIONBY: NEWMAN

OPINION: [*1350] NEWMAN, Circuit Judge.

Both of the parties to a patent interference proceeding have appealed the decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office, wherein the Board held that the specification of neither party met the written description requirement of the patent statute. Capon v. Eshhar, Interf. No. 103,887 (Bd. Pat. App. & Interf. Mar. 26, 2003). The Board dissolved the interference and cancelled all [**2] of the claims of both parties corresponding to the interference count. With this ruling, the Board terminated the proceeding and did not reach the question of priority of invention. We conclude that the Board erred in its application of the law of written description. The decision is vacated and the case is remanded to the Board for further proceedings.

BACKGROUND

Daniel J. Capon, Arthur Weiss, Brian A. Irving, Margo R. Roberts, and Krisztina Zsebo (collectively "Capon") and Zelig Eshhar, Daniel Schindler, Tova Waks, and [*1351] Gideon Gross (collectively "Eshhar") were the parties to an interference proceeding between Capon's *United States Patent No. 6,407,221* ("the *'221 patent*") entitled "Chimeric Chains for Receptor-Associated Signal Transduction Pathways" and Eshhar's patent application Serial No. 08/084,994 ("the '994 application") entitled "Chimeric Receptor Genes and Cells Transformed Therewith." Capon's *Patent No. 5,359,046* ("the '046 patent"), parent of the *'221 patent*, was also included in the interference but was held expired for non-payment of a maintenance fee. The PTO included the *'046* patent in its decision and in its argument of this appeal. n1

n1 Although Capon is designated as appellant and Eshhar as cross-appellant, both appealed the Board's decision. See *Fed. R. App. P. 28(h)*. The Director of the PTO intervened to support the Board, and has fully participated in this appeal.

[**3]

A patent interference is an administrative proceeding pursuant to *35 U.S.C. § § 102(g)* and *135(a)*, conducted for the purpose of determining which of competing applicants is the first inventor of common subject matter. An interference is instituted after the separate patent applications have been examined and found to contain patentable subject matter. Capon's patents had been examined and had issued before this interference was instituted, and Eshhar's application had been examined and allowed but a patent had not yet issued.

During an interference proceeding the Board is authorized to determine not only priority of invention but also to redetermine patentability. *35 U.S.C. § 6(b)*. The question of patentability of the claims of both parties was raised *sua sponte* by an administrative patent judge during the preliminary proceedings. Thereafter the Board conducted an *inter partes* proceeding limited to this question, receiving evidence and argument. The Board then invalidated all of the claims that had been designated as corresponding to the count of the interference, viz., all of the claims of the Capon *'221 patent*, claims 5-8 of [**4] the Capon *'046* patent, and claims 1-7, 9-20, and 23 of the Eshhar '994 application.

[HN1] In accordance with the Administrative Procedure Act, the law as interpreted and applied by the agency receives plenary review on appeal, and the agency's factual findings are reviewed to determine whether they were arbitrary, capricious, or unsupported by substantial evidence in the administrative record. See *5 U.S.C. § 706(2)*; *Dickinson v. Zurko, 527 U.S. 150, 164-65, 144 L. Ed. 2d 143, 119 S. Ct. 1816 (1999)*; *In re Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000)*.

The Invention

A chimeric gene is an artificial gene that combines segments of DNA in a way that does not occur in nature. The *'221 patent* and '994 application are directed to the production of chimeric genes designed to enhance the immune response by providing cells with specific cell-surface antibodies in a form that can penetrate diseased sites, such as solid tumors, that were not previously reachable. The parties explain that their invention is a way of endowing immune cells with antibody-type specificity, by combining known antigen-binding-domain producing DNA and known lymphocyte-receptor-protein [**5] producing DNA into a unitary gene that can express a unitary polypeptide chain. Eshhar summarized the problem to which the invention is directed:

> Antigen-specific effector lymphocytes, such as tumor-specific T cells, are very rare, individual-specific, limited in their recognition spectrum and difficult to obtain against most malignancies. Antibodies, on the other hand, are readily [*1352] obtainable, more easily derived, have wider spectrum and are not individual-specific. The major problem of applying specific antibodies for cancer immunotherapy lies in the inability of sufficient amounts of monoclonal antibodies (mAb) to reach large areas within solid tumors.

Technical Paper Explaining Eshhar's Invention, at 6.

The inventions of Capon and Eshhar are the chimeric DNA that encodes single-chain chimeric proteins for expression on the surface of cells of the immune system, plus expression vectors and cells transformed by the chimeric DNA. The experts for both parties explain that the invention combines selected DNA segments that are both endogenous and nonendogenous to a cell of the immune system, whereby the nonendogenous segment encodes the single-chain variable ("scFv") [**6] domain of an antibody, and the endogenous segment encodes cytoplasmic, transmembrane, and extracellular domains of a lymphocyte signaling protein. They explain that the scFv domain combines the heavy and light variable ("Fv") domains of a natural antibody, and thus has the same specificity as a natural antibody. Linking this single chain domain to a lymphocyte signaling protein creates a chimeric scFv-receptor ("scFvR") gene which, upon transfection into a cell of the immune system, combines the specificity of an antibody with the tissue penetration, cytokine production, and target-cell destruction capability of a lymphocyte.

The parties point to the therapeutic potential if tumors can be infiltrated with specifically designed immune cells of appropriate anti-tumor specificity.

The Eshhar Claims

The Board held unpatentable the following claims of Eshhar's '994 application; these were all of the '994 claims that had been designated as corresponding to the count of the interference. Eshhar's claim 1 was the designated count.

> 1. A chimeric gene comprising

a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and

a second gene segment [**7] encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein

wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells,

which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFV domain binds to its antigen.

2. A chimeric gene according to claim 1 wherein the second gene segment further comprises partially or entirely the extracellular domain of said endogenous protein.

3. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against tumor cells.

4. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against virus infected cells.

5. A chimeric gene according to claim 4 wherein the virus is HIV.

6. [**8] A chimeric gene according to claim 1 wherein the second gene segment encodes a lymphocyte receptor chain.

[*1353] 7. A chimeric gene according to claim 6 wherein the second gene segment encodes a chain of the T cell receptor.

9. A chimeric gene according to claim 7 wherein the second gene segment encodes the a, B, y, or o chain of the antigen-specific T cell receptor.

10. A chimeric gene according to claim 1 wherein the second gene segment encodes a polypeptide of the TCR/CD3 complex.

11. A chimeric gene according to claim 10 wherein the second gene segment encodes the zeta or eta isoform chain.

12. A chimeric gene according to claim 1 wherein the second gene segment encodes a subunit of the Fc receptor or IL-2 receptor.

13. A chimeric gene according to claim 12 wherein the second gene segment encodes a common subunit of IgE and IgG binding Fc receptors.

14. A chimeric gene according to claim 13 wherein said subunit is the gamma subunit.

15. A chimeric gene according to claim 13 wherein the second gene segment encodes the CD16a chain of the FcyRIII or FcyRII.

16. A chimeric gene according to claim 12 wherein the second gene segment encodes the a [**9] or B subunit of the IL-2 receptor.

17. An expression vector comprising a chimeric gene according to claim 1.

18. A cell of the immune system endowed with antibody specificity transformed with an expression vector according to claim 17.

19. A cell of the immune system endowed with antibody specificity comprising a chimeric gene according to claim 1.

20. A cell if the immune system according to claim 19 selected from the group consisting of a natural killer cell, a lymphokine activated killer cell, a cytotoxic T cell, a helper T cell and a subtype thereof.

23. A chimeric gene according to claim 1 wherein said endogenous protein is a lymphocyte receptor chain, a polypeptide of the TCR/CD3 complex, or a subunit of the Fc or IL-2 receptor.

The Board did not discuss the claims separately, and held that the specification failed to satisfy the written description requirement as to all of these claims.

The Capon Claims

Claims 1-10, all of the claims of the *'221 patent*, were held unpatentable on written description grounds. Claims 1-6 are directed to the chimeric DNA, claims 7, 8, and 10 to the corresponding cell comprising the DNA, and claim 9 to [**10] the chimeric protein:

> 1. A chimeric DNA encoding a membrane bound protein, said chimeric DNA comprising in reading frame:
>
> DNA encoding a signal sequence which directs said membrane bound protein to the surface membrane;
>
> DNA encoding a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell or a viral protein;
>
> DNA encoding a transmembrane domain which is obtained from a protein selected from the group consisting of CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and
>
> DNA encoding a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,
>
> [*1354] wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric DNA is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein [**11] initiates signaling in said host cell when said extracellular domain binds said at least one ligand.
>
> 2. The DNA of claim 1, wherein said single-chain antibody recognizes an antigen selected from the group consisting of viral antigens and tumor cell associated antigens.
>
> 3. The DNA of claim 2 wherein said single-chain antibody is specific for the HIV env glycoprotein.
>
> 4. The DNA of claim 1, wherein said transmembrane domain is naturally joined to said cytoplasmic domain.
>
> 5. An expression cassette comprising a transcriptional initiation region, the DNA of claim 1 under the transcriptional control of said transcriptional initiation region, and a transcriptional termination region.
>
> 6. A retroviral RNA or DNA construct comprising the expression cassette of claim 5.
>
> 7. A cell comprising the DNA of claim 1.
>
> 8. The cell of claim 7, wherein said cell is a human cell.
>
> 9. A chimeric protein comprising in the N-terminal to C-terminal direction:
>
> a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell [**12] or a viral protein;
>
> a transmembrane domain which is obtained from a protein selected from the group consisting CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and
>
> a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,
>
> wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric protein is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said ex-

> tracellular domain binds said at least one ligand.
>
> 10. A mammalian cell comprising as a surface membrane protein, the protein of claim 9.

In addition, claims 5, 6, 7, and 8 of Capon's *'046* patent were held unpatentable. These claims are directed to chimeric DNA sequences where the encoded extracellular domain is a single-chain antibody containing ligand binding activity.

The Board Decision

The Board presumed [**13] enablement by the specifications of the *'221 patent* and '994 application of the full scope of their claims, and based its decision solely on the ground of failure of written description. The Board held that neither party's specification provides the requisite description of the full scope of the chimeric DNA or encoded proteins, by reference to knowledge in the art of the "structure, formula, chemical name, or physical properties" of the DNA or the proteins. In the Board's words:

> [*1355] We are led by controlling precedent to understand that the full scope of novel chimeric DNA the parties claim is not described in their specifications under *35 U.S.C. § 112*, first paragraph, by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences which encode many protein domains, which comprise single-chain proteins and/or DNA constructs made in accordance with the plans, schemes, and examples thereof the parties disclose.

Bd. op. at 4. As controlling precedent the Board cited *Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997)*; [**14] *Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993)*; *Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed. Cir. 1991)*; and *Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316 (Fed. Cir. 2002)*. The Board summarized its holding as follows:

> Here, both Eshhar and Capon claim novel genetic material described in terms of the functional characteristics of the protein it encodes. Their specifications do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results.

Bd. op. at 89.

DISCUSSION

Eshhar and Capon challenge both the Board's interpretation of precedent and the Board's ruling that their descriptions are inadequate. Both parties explain that their chimeric genes are produced by selecting and combining known heavy-and light-chain immune-related DNA segments, using known DNA-linking procedures. The specifications of both parties describe procedures for identifying [**15] and obtaining the desired immune-related DNA segments and linking them into the desired chimeric genes. Both parties point to their specific examples of chimeric DNA prepared using identified known procedures, along with citation to the scientific literature as to every step of the preparative method.

The parties presented expert witnesses who placed the invention in the context of prior knowledge and explained how the descriptive text would be understood by persons of skill in the field of the invention. The witnesses explained that the principle of forming chimeric genes from selected segments of DNA was known, as well as their methods of identifying, selecting, and combining the desired segments of DNA. Dr. Eshhar presented an expert statement wherein he explained that the prior art contains extensive knowledge of the nucleotide structure of the various immune-related segments of DNA; he stated that over 785 mouse antibody DNA light chains and 1,327 mouse antibody DNA heavy chains were known and published as early as 1991. Similarly Capon's expert Dr. Desiderio discussed the prior art, also citing scientific literature:

> The linker sequences disclosed in the *'221 patent* [**16] (col. 24, lines 4 and 43) used to artificially join a heavy and light chain nucleic acid sequence and permit functional association of the two ligand binding regions were published by 1990, as were

> the methods for obtaining the mature sequences of the desired heavy and light chains for constructing a SAb (Exhibit 47, Batra et al., J., Biol. Chem., 1990; Exhibit 48, Bird et al., Science, 1988; Exhibit 50, Huston et al., PNAS, [*1356] 1988; Exhibit 51, Chaudhary, PNAS, 1990, Exhibit 56, Morrison et al., Science, 1985; Exhibit 53, Sharon et al., Nature 1984).

Desiderio declaration at 4 P11.

Both parties stated that persons experienced in this field would readily know the structure of a chimeric gene made of a first segment of DNA encoding the single-chain variable region of an antibody, and a second segment of DNA encoding an endogenous protein. They testified that re-analysis to confirm these structures would not be needed in order to know the DNA structure of the chimeric gene, and that the Board's requirement that the specification must reproduce the "structure, formula, chemical name, or physical properties" of these DNA combinations had been overtaken by the state of the science. [**17] They stated that where the structure and properties of the DNA components were known, re-analysis was not required.

Eshhar's specification contains the nucleotide sequences of sixteen different receptor primers and four different scFv primers from which chimeric genes encoding scFvR may be obtained, while Capon's specification cites literature sources of such information. Eshhar's specification shows the production of chimeric genes encoding scFvR using primers, as listed in Eshhar's Table I. Capon stated that natural genes are isolated and joined using conventional methods, such as the polymerase chain reaction or cloning by primer repair. Capon, like Eshhar, discussed various known procedures for identifying, obtaining, and linking DNA segments, accompanied by experimental examples. The Board did not dispute that persons in this field of science could determine the structure or formula of the linked DNA from the known structure or formula of the components.

The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than [**18] the specific examples. Eshhar and Capon each responds by pointing to the scientific completeness and depth of their descriptive texts, as well as to their illustrative examples. The Board did not relate any of the claims, broad or narrow, to the examples, but invalidated all of the claims without analysis of their scope and the relation of claim scope to the details of the specifications.

Eshhar and Capon both argue that they have set forth an invention whose scope is fully and fairly described, for the nucleotide sequences of the DNA in chimeric combination is readily understood to contain the nucleotide sequences of the DNA components. Eshhar points to the general and specific description in his specification of known immune-related DNA segments, including the examples of their linking. Capon points similarly to his description of selecting DNA segments that are known to express immune-related proteins, and stresses the existing knowledge of these segments and their nucleotide sequences, as well as the known procedures for selecting and combining DNA segments, as cited in the specification.

Both parties argue that the Board misconstrued precedent, and that precedent does not establish [**19] a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures.

The Statutory Requirement

[HN2] The required content of the patent specification is set forth in *Section 112 of Title 35*:

> *§ 112* P1. The specification shall contain a written description of the invention, [*1357] and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[HN3] The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. See *Enzo Biochem, 296 F.3d at 1330* (the written description requirement "is the quid pro quo [**20] of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time"); *Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345-46 (Fed. Cir. 2000)* (the purpose of the written description requirement "is to ensure that the scope of the right to exclude ...does not overreach the scope of the inventor's contribution to the field of art as described in

the patent specification"); *In re Barker, 559 F.2d 588, 592 n. 4 (CCPA 1977)* (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented [**21] advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known. In *Lilly, 119 F.3d at 1567*, the cDNA for human insulin had never been characterized. Similarly in *Fiers, 984 F.2d at 1171*, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen, 927 F.2d at 1206*, the court explained that a novel gene was [**22] not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In *Enzo Biochem, 296 F.3d at 1326*, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003)* the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in *Noelle* [*1358] *v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004)*, where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in *University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 925-26 (Fed. Cir. 2004)*, where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.

The "written description" [**23] requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern [**24] the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Claim Scope

There remains the question of whether the specifications adequately support the breadth of all of the claims that are presented. The Director argues that it cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and that the claims are too broad because they may include inoperative species. The inventors say that they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention. They state that biological properties typically vary, and that their specifications provide for evaluation of the effectiveness [**25] of their chimeric combinations.

[HN4] It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the

coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. See, e.g., *Enzo Biochem, 296 F.3d at 1327-28* (remanding for district court to determine "whether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); *Lilly, 119 F.3d at 1569* (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus" had not been provided); *In re Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989)* (two chemical compounds were insufficient [*1359] description of subgenus); *In re Smith, 59 C.C.P.A. 1025, 458 F.2d 1389, 1394-95 (CCPA 1972)* (disclosure of genus and one species was not sufficient description of intermediate subgenus); *In re Grimme, 47 C.C.P.A. 785, 274 F.2d 949, 952, 1960 Dec. Comm'r Pat. 123 (CCPA 1960)* (disclosure of single example and [**26] statement of scope sufficient disclosure of subgenus).

Precedent illustrates that [HN5] the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. See, e.g., *In re Wallach, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004)* (an amino acid sequence supports "the entire genus of DNA sequences" that can encode the amino acid sequence because "the state of the art has developed" such that it is a routine matter to convert one to the other); *University of Rochester, 358 F.3d at 925* (considering whether the patent disclosed the compounds necessary to practice the claimed method, given the state of technology); *Singh v. Brake, 317 F.3d 1334, 1343, 48 Fed. Appx. 766 (Fed. Cir. 2002)* (affirming adequacy of disclosure by distinguishing precedent in which the selection of a particular species within the claimed genus had involved "highly unpredictable results").

[HN6] It [**27] is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *In re Angstadt, 537 F.2d 498, 504 (CCPA 1976)* ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both Eshhar and Capon present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes. For example, Eshhar points out that in Example 1 of his specification the FcR . chain was used, which chain was amplified from a human cDNA clone, using the procedure of Kuster, H. et al., J. Biol. Chem., 265:6448-6451 (1990), which is cited in the specification and reports the complete sequence of the FcRy chain. Eshhar's Example 1 also explains the source of the genes that provide the heavy and light chains of the single chain antibody, [**28] citing the PhD thesis of Gideon Gross, a co-inventor, which cites a reference providing the complete sequence of the Sp6 light chain gene used to construct the single-chain antibody. Eshhar states that the structure of the Sp6 heavy chain antibody was well known to those of skill in the art and readily accessible on the internet in a database as entry EMBL: MMSP6718. Example 5 at page 54 of the Eshhar specification cites Ravetch et al., J. Exp. Med., 170:481-497 (1989) for the method of producing the CD16 a DNA clone that was PCR amplified; this reference published the complete DNA sequence of the CD16 a chain, as discussed in paragraph 43 of the Eshhar Declaration. Example 3 of the Eshhar specification uses the DNA of the monoclonal anti-HER2 antibody and states that the N29 hybridoma that produces this antibody was deposited with the Collection Nationale de Cultures de Microorganismes, Institut Pasteur, Paris, on August 19, 1992, under Deposit No. CNCM I-1262. It is incorrect to criticize the methods, examples, and referenced prior art of the Eshhar specification as but "a few PCR primers and probes," as does the Director's brief.

[*1360] Capon's Example 3 provides a detailed description [**29] of the creation and expression of single chain antibody fused with T-cell receptor zeta chain, referring to published vectors and procedures. Capon, like Eshhar, describes gene segments and their ligation to form chimeric genes. Although Capon includes fewer specific examples in his specification than does Eshhar, both parties used standard systems of description and identification, as well as known procedures for selecting, isolating, and linking known DNA segments. Indeed, the Board's repeated observation that the full scope of all of the claims appears to be "enabled" cannot be reconciled with the Board's objection that only a "general plan" to combine unidentified DNA is presented. See *In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988)* (experimentation to practice invention must not be "undue" for invention to be considered enabled).

The PTO points out that for biochemical processes relating to gene modification, protein expression, and immune response, success is not assured. However, generic inventions are not thereby invalid. Precedent distinguishes among generic inventions that are adequately supported, those that are merely a "wish" or "plan," the words of [**30] *Fiers v. Revel, 984 F.2d at 1171*, and those in between, as illustrated by *Noelle v. Lederman, 355 F.3d at 1350*; the facts of the specific case must be

evaluated. The Board did not discuss the generic concept that both Capon and Eshhar described -- the concept of selecting and combining a gene sequence encoding the variable domain of an antibody and a sequence encoding a lymphocyte activation protein, into a single DNA sequence which, upon expression, allows for immune responses that do not occur in nature. The record does not show this concept to be in the prior art, and includes experimental verification as well as potential variability in the concept.

Whether the inventors demonstrated sufficient generality to support the scope of some or all of their claims, must be determined claim by claim. The Board did not discuss the evidence with respect to the generality of the invention and the significance of the specific examples, instead simply rejecting all the claims for lack of a complete chimeric DNA sequence. As we have discussed, that reasoning is inapt for this case. The Board's position that the patents at issue were merely an "invitation to [**31] experiment" did not distinguish among the parties' broad and narrow claims, and further concerns enablement more than written description. See *Adang v. Fischhoff, 286 F.3d 1346, 1355 (Fed. Cir. 2002)* (enablement involves assessment of whether one of skill in the art could make and use the invention without undue experimentation); *In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)* (same). [HN7] Although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements.

[HN8] The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. Our predecessor court summarized in *In re Storrs, 44 C.C.P.A. 981, 245 F.2d 474, 478, 1957 Dec. Comm'r Pat. 361 (CCPA 1957)* that "it must be borne in mind that, while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due regard to the subject matter involved." This aspect may [**32] warrant exploration on remand.

In summary, the Board erred in ruling that *§ 112* imposes a *per se* rule requiring recitation in the specification of the nucleotide [*1361] sequence of claimed DNA, when that sequence is already known in the field. However, the Board did not explore the support for each of the claims of both parties, in view of the specific examples and general teachings in the specifications and the known science, with application of precedent guiding review of the scope of claims.

We remand for appropriate further proceedings.

VACATED AND REMANDED

Current Opinion in Immunology
Volume 9, Issue 2 , April 1997, Pages 201-212

doi:10.1016/S0952-7915(97)80136-7 Cite or Link Using DOI

Antibody engineering

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Available online 11 February 2002.

Abstract

The development of recombinant techniques for the rapid cloning, expression, and characterization of cDNAs encoding antibody (Ab) subunits has revolutionized the field of antibody engineering. By fusion to heterologous protein domains, chain shuffling, and inclusion of self-assembly motifs, novel molecules such as bispecific Abs can now be generated which possess the subset of functional properties designed to fit the intended application. Rapid technological developments in phage display of peptides and proteins have led to a plethora of applications directed towards immunology and antibody engineering. Many of the problems associated with the therapeutic use of Abs are being addressed by the application of these new techniques.

Abbreviations: **Ab** antibody; **CDR** complementarity determining region; **EPO** erythropoietin; **ES** embryonic stem; **IL** interleukin; **m** monoclonal; **PCR** polymerase chain reaction; **SC** single chain; **V** variable; **YAC** yeast artificial chromosome

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1: Crit Rev Immunol. 1992;12(3-4):125-68. Related Articles, Links

Genetically engineered antibodies: progress and prospects.

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Techniques of genetic engineering and expression have been applied to the production of antibodies in a variety of expression systems. Novel antibodies have been produced with a variety of modifications: as chimeric antibodies, as "humanized" antibodies, with catalytic groups, as bifunctional or fusion proteins, and as functional fragments such as Fabs or Fvs. The domain structure of the antibody is favorable to such manipulation; the novel proteins often retain their antibody-derived activity and acquire new properties as well. Chimeric and complementarity-determining region (CDR)-grafted antibodies have been effective in immunotherapy, but problems of immunogenicity remain. Combinatorial libraries produced in bacteriophage may present an alternative to animal immunization as a source of antigen-binding specificities. Structural and mutational analysis of variable regions is providing useful information about the requirements of the variable region for antigen binding. Careful analysis and comparison of effector functions among immunoglobulin isotypes may be applied to the design of effective therapeutic antibodies.

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1: Clin Chem. 1988 Sep;34(9):1668-75. Related Articles, Links

Production and characterization of genetically engineered antibody molecules.

Morrison SL, Canfield S, Porter S, Tan LK, Tao MH, Wims LA.

Department of Microbiology, Columbia University College of Physicians and Surgeons, New York, NY 10032.

Expression of antibody heavy- and light-chain genes by transfection permits the production of monoclonal antibodies with improved biological and antigen-binding properties. The immunoglobulin genes are placed in vectors containing a gene for encoding a protein that provides a biochemically selectable function in eukaryotic cells; these vectors are transfected into myeloma and hybridoma cells. Selection of drug-resistant cells permits the efficient isolation of the rare cells that express the transfected DNA. By placing heavy and light chains on plasmids with different selectable markers, one can deliver heavy- and light-chain genes simultaneously to the same cell. The transfected immunoglobulin genes are efficiently expressed and the proteins produced are a faithful mirror of the genes that were introduced. Using the standard techniques of genetic engineering and gene transfection, we can now produce antibodies of widely varying structures, including chimeric antibodies with segments derived from different species. These antibodies provide useful reagents to study structure-function relationships within the antibody molecule. Ultimately it will be possible to produce a new generation of antibody molecules with improved antigen-binding properties and effector functions.

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1: Nature. 1991 Jan 24;349(6307):293-9. Related Articles, Links

nature

Man-made antibodies.

Winter G, Milstein C.

MRC Laboratory of Molecular Biology, Cambridge, UK.

Monoclonal antibodies can now be genetically engineered and endowed with new properties. In the future, gene technology could enable antigen-binding fragments to be made by exploiting repertoires of variable domain genes derived from immunized animals and expressed in bacteria. How readily can this approach be extended to production of 'in vitro' repertoires of variable domain genes, and obviate the immunization of animals?

Publication Types:

- Review

PMID: 1987490 [PubMed - indexed for MEDLINE]

☐ 1: Tissue Antigens. 1996 Jan;47(1):1-20. Related Articles, Links

Rapid and reliable cloning of antibody variable regions and generation of recombinant single chain antibody fragments.

Gilliland LK, Norris NA, Marquardt H, Tsu TT, Hayden MS, Neubauer MG, Yelton DE, Mittler RS, Ledbetter JA.

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Single chain antibody variable region fragments (sFv), by virtue of their size and method of construction are potentially useful as therapeutic reagents and as tools for exploring cell surface receptor function. sFv offer several advantages over the intact immunoglobulin molecule. For instance, they are expressed from a single transcript and can be molecularly linked to other proteins to generate bispecific sFv molecules or single-chain immunotoxins. The relatively small size of sFv is an advantage in allowing for easier penetrance into tissue spaces, and their clearance rate is exceedingly rapid. sFv are useful for gene therapy since they can be directed to a specific cellular localization and can be fused to retroviral env genes to control viral host range. To prepare sFv to murine and human leukocyte CD antigens, we devised a method for rapid cloning and expression that can yield functional protein within 2-3 weeks of RNA isolation from hybridoma cells. The variable regions were cloned by poly-G tailing the first strand cDNA followed by anchor PCR with a forward poly-C anchor primer and a reverse primer specific for constant region sequence. Both primers contain flanking restriction sites for insertion into PUC19. Sets of PCR primers for isolation of murine, hamster and rat VL and VH genes were generated. Following determination of consensus sequences for a specific VL and VH pair, the VL and VH genes were linked by DNA encoding an intervening peptide linker [usually (Gly4Ser)3] and the VL-link-VH gene cassettes were transferred into the pCDM8 mammalian expression vector. The constructs were transfected into COS cells and sFvs were recovered from spent culture supernatant. We have used this method to generate functional sFv to human CD2, CD3, CD4, CD8, CD28, CD40, CD45 and to murine CD3 and gp39, from hybridomas producing murine, rat, or hamster antibodies. Initially, the sFvs were expressed as fusion proteins with the hinge-CH2-CH3 domains of

human IgG1 to facilitate rapid characterization and purification using goat anti-human IgG reagents or protein A. We also found that active sFv could be expressed with a small peptide > or = tag > or = or in a tail-less form. Expression of CD3 (G19-4) sFv tail-less or Ig tailed forms demonstrated increased cellular signalling activity and suggested that sFv have potential for activating receptors.

PMID: 8929708 [PubMed - indexed for MEDLINE]

1: J Immunol. 1986 Aug 1;137(3):1066-74. Related Articles, Links

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- J Immunol. 1990 Nov 1;145(9):3150.

A genetically engineered murine/human chimeric antibody retains specificity for human tumor-associated antigen.

Sahagan BG, Dorai H, Saltzgaber-Muller J, Toneguzzo F, Guindon CA, Lilly SP, McDonald KW, Morrissey DV, Stone BA, Davis GL, et al.

Chimeric immunoglobulin genes were constructed by fusing murine variable region exons to human constant region exons. The ultimate goal was to produce an antibody capable of escaping surveillance by the human immune system while retaining the tumor specificity of a murine monoclonal. The murine variable regions were isolated from the functionally expressed kappa and gamma 1 immunoglobulin genes of the murine hybridoma cell line B6.2, the secreted monoclonal antibody of which reacts with a surface antigen from human breast, lung, and colon carcinomas. The kappa and gamma 1 chain fusion genes were co-introduced into non-antibody producing murine myeloma cells by electroporation. Transfectants that produced murine/human chimeric antibody were obtained at high frequency as indicated by immunoblots probed with an antisera specific for human immunoglobulin. Enzyme-linked immunoabsorbent assay analysis demonstrated that this chimeric antibody was secreted from the myeloma cells and retained the ability to bind selectively to membrane prepared from human tumor cells. The chimeric immunoglobulin was also shown by indirect fluorescence microscopy to bind to intact human carcinoma cells with specificity expected of B6.2. The ability of chimeric antibody to recognize human tumor-associated antigen makes feasible a novel approach to cancer immunotherapy.

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1: J Immunol Methods. 1994 Feb 10;168(2):149-65. Related Articles, Links

The genetic engineering of monoclonal antibodies.

Owens RJ, Young RJ.

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A number of recent technological developments have greatly facilitated the genetic engineering of immunoglobulins. The use of PCR has permitted the variable regions to be rapidly cloned either from a specific hybridoma source or as a gene library from non-immunised cells. The conversion of the rodent antibody into a humanized version is now well established. To develop these antibodies for clinical use has required the development of high level expression systems. For the expression of large multimeric glycoproteins, mammalian cell systems generally provide the highest levels of secreted product and therefore are the methods of choice for producing whole recombinant antibodies. Novel antigen-binding units have been developed by joining the two variable domains of an antibody into single-chain polypeptides. Such fragments can be produced in high yield by secretion from E. coli raising the prospect of bulk preparation of these antibody fragments for the development of low-cost immunopurification and assay reagents. Finally, the ability to screen for antigen binding by displaying immunoglobulin variable regions on the surface of filamentous bacteriaphages has opened up the possibility of bypassing the immune system to generate novel antibody specificities in vitro.

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Production and characterization of genetically engineered antibody molecules.

Morrison SL, Canfield S, Porter S, Tan LK, Tao MH, Wims LA.

Department of Microbiology, Columbia University College of Physicians and Surgeons, New York, NY 10032.

Expression of antibody heavy- and light-chain genes by transfection permits the production of monoclonal antibodies with improved biological and antigen-binding properties. The immunoglobulin genes are placed in vectors containing a gene for encoding a protein that provides a biochemically selectable function in eukaryotic cells; these vectors are transfected into myeloma and hybridoma cells. Selection of drug-resistant cells permits the efficient isolation of the rare cells that express the transfected DNA. By placing heavy and light chains on plasmids with different selectable markers, one can deliver heavy- and light-chain genes simultaneously to the same cell. The transfected immunoglobulin genes are efficiently expressed and the proteins produced are a faithful mirror of the genes that were introduced. Using the standard techniques of genetic engineering and gene transfection, we can now produce antibodies of widely varying structures, including chimeric antibodies with segments derived from different species. These antibodies provide useful reagents to study structure-function relationships within the antibody molecule. Ultimately it will be possible to produce a new generation of antibody molecules with improved antigen-binding properties and effector functions.

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1: Hum Antibodies Hybridomas. 1992 Jul;3(3):137-45. Related Articles, Links

Preparation of genetically engineered monoclonal antibodies for human immunotherapy.

Parren PW.

Central Laboratory, The Netherlands Red Cross Blood Transfusion Service, Amsterdam.

Production of human monoclonal antibodies (MAbs) of predefined specificity using conventional hybridoma technology has proved to be difficult. Immunotherapeutic intervention in humans with rodent MAbs, however, is disadvantageous because of the antigenicity of these proteins and may result in human antibody responses against this foreign agent. To circumvent this problem, recombinant DNA techniques have been developed to transplant the specificity of a rodent MAb into a human antibody. Two basic approaches are being employed: first, combining rodent MAb variable regions with human constant regions; and more recently, "reshaping" human MAbs by grafting complementarity-determining regions (CDR) into the human antibody framework. These humanized MAbs can now be used to study human Fc-dependent effector mechanisms in detail, which seems essential to optimize potential in vivo application.

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